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(54) Title: TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

(57) Abstract: Two novel cAMP-specific isoforms of rat PDE4B are disclosed. pRPDE90 is a cDNA encoding a 659-amino acid-long protein with a large region corresponding to similar regions found in PDE4B1 and PDE4B3. It is separated from these isoforms by a 17-amino acid region found at its extreme amino-terminal end which shows no homology to any previously-cloned sequence. pRPDE89 is a rat cDNA which encodes a 726-amino acid-long protein which is 96 % identical to the human PDE4B1 phosphodiesterase isoform.

WO 01/44449 A1

TWO NOVEL cAMP-SPECIFIC PHOSPHODIESTERASE (PDE4B) ISOFORMS AND RELATED TECHNOLOGY

1. Related Applications

5 This application is related to and claims the benefit of United States Provisional Application Serial No. 60/170,562 of Graeme B. Bolger, filed December 14, 1999 and entitled "Two Novel cAMP-Specific Phosphodiesterase (PDE4B) Isoforms and Related Technology," which is incorporated herein by reference.

10 2. Field of the Invention

The present invention relates to cyclic AMP-specific phosphodiesterases (PDE4 enzymes), which help regulate physiological processes by hydrolyzing cAMP, an intracellular signaling molecule. Specifically, the invention relates to two novel cAMP-specific phosphodiesterase isoforms which are expressed in many body tissues, including
15 the brain.

3. Technical Background

Cyclic AMP ("cAMP") is an intracellular signaling molecule involved in many important cellular processes. Specifically, cAMP is critical to signaling pathways which
20 regulate physiological processes such as those involved in vascular smooth muscle, the immune system, and the brain. cAMP-specific phosphodiesterases, referred to as "PDE4 enzymes," hydrolyze cAMP and thus regulate these pathways in cells. The cAMP-specific phosphodiesterases can be differentiated from other cyclic nucleotide phosphodiesterase ("PDE") families by sequence homology in the catalytic region of the
25 proteins as well as by their ability to be inhibited by a specific class of drugs, such as rolipram. Beavo, *Physiol. Rev.* 75:725-48 (1995). Rolipram and other specific PDE4 inhibitors have anti-depressant, anti-inflammatory and smooth muscle relaxant properties in humans. Houslay et al., *Advances in Pharmacology*, 44:225-342 (1998). PDE4 enzymes are also characterized by the presence of unique "signature" regions of sequence,
30 called upstream conserved regions, or "UCR," such as UCR1 and UCR2, which are located in the amino-terminal third of the proteins. Houslay, et al., *supra*; Bolger et al., *Mol. Cell Biol.*, 13:6558-71 (1993).

PDE4 enzymes are also the closest vertebrate homologs of the *dunce* gene of *Drosophila melanogaster*, which was isolated as a mutation affecting learning and memory. Davis, *Physiol. Rev.* 76:299–317 (1996). The mammalian PDE4s are encoded by four genes (*PDE4A*, *PDE4B*, *PDE4C* and *PDE4D*), and it has been shown by several researchers that additional diversity in this family is produced by alternative mRNA splicing. Bolger et al., *supra*; Sette et al., *J. Biol. Chem.*, 269(32):20806 (Aug. 12, 1994); Bolger et al., *J. Biol. Chem.*, 271:1065–71 (1996); Bolger et al., *Biochem. J.*, 328:539–48 (1997); Naro et al., *Endocrinology*, 137:2464–72 (1996); Huston et al., *Biochem J.* 328:549–56 (1997). See Houslay et al., *supra*, for a review of these findings. Often the alternatively-spliced isoforms have different tissue expression patterns, a fact which suggests that each may have a distinct function.

Intracellular signaling molecules are important since they transmit a signal received outside of the cell to target molecules in the cytosol, thus allowing a cell to react to changes in its environment. This transmission is generally a multistep process often having at least the general steps laid out in the following cAMP-specific sequence: First, an extracellular ligand binds to a plasma membrane-bound receptor molecule which has a binding domain extending into the extracellular space and a domain extending into the cytosol. Second, the binding of the ligand to the extracellular domain changes the conformation of the cytosolic domain, thus causing it to bind to a G-protein. Third, the G-protein, in turn, activates a plasma membrane enzyme which produces cAMP (adenylyl cyclase). Fourth, the cAMP then binds to target molecules in the cytosol, thus altering their conformation and activity. Finally, cyclic AMP-specific phosphodiesterases rapidly break down the cAMP, hydrolizing it to form adenosine 5'-monophosphate.

As seen in the final step, in order to use cAMP as a signaling molecule, a cell must be able to quickly manipulate the levels of cAMP present in response to signals transmitted to the outside of the cell. Cyclic AMP functions well in this respect, having been shown in some cases to respond to hormonal stimulation by increasing in cellular concentration by five-fold within seconds.

Such rapid changes in cAMP levels are possible due to a cell's ability to rapidly synthesize cAMP. Cells are also adapted to rapidly break down cAMP. Cyclic AMP is synthesized from ATP by adenylyl cyclase, an enzyme found in the plasma membrane of a cell. Cyclic AMP is hydrolized by cyclic AMP phosphodiesterases to form adenosine

5'-monophosphate ("5'-AMP"). These phosphodiesterases are found in many tissues, including specific regions of the brain.

It is known that certain cAMP-specific phosphodiesterases ("PDE4 enzymes") are the targets of inhibitors. Some of these inhibitors have been shown to have positive effects on the brain, including exhibiting anti-depressant properties, memory-enhancing qualities, and other positive effects on the function of the central nervous system. Unfortunately, however, these beneficial effects are often accompanied by nausea and other gastrointestinal side effects. These negative side effects are likely mediated at least in part by the action of the inhibitors used on the brain. The number of isoforms of the PDE4 enzymes present in the brain is currently unknown, as is an understanding of which inhibitors affect which phosphodiesterases. Knowledge of novel isoforms of PDE4 enzymes would be a great advancement in the art, allowing researchers and health professionals to learn to target PDE4 inhibitors to specific isoforms and limit the effects of the inhibition to the desired, positive effects, while avoiding inhibition of those isoforms whose inhibition causes the deleterious side effects noted above.

From the foregoing, it will be appreciated that it would be an advancement in the art to identify additional PDE4 enzyme isoforms. Such identification would enable investigation of the patterns of isoform tissue expression, and thus allow selective targeting of specific isoforms with isoform-specific inhibitors, yielding effective use of the beneficial effects of inhibition while avoiding the deleterious ones.

Such novel PDE4 enzyme isoforms are disclosed herein.

4. Brief Summary of the Invention:

The present invention relates to isoforms of cAMP-specific phosphodiesterase. Specifically, two rat cDNAs, pRPDE89 and pRPDE90, were isolated from a rat cerebral cortex cDNA library. Both of these were found to encode novel PDE4B isoforms. The invention thus comprises a first cDNA, pRPDE89, which encodes a protein identical in length to that encoded by the previously-described human PDE4B1 isoform known in the art. The protein encoded by both the rat and human genetic material is 736 amino acids in length. This rat cAMP-specific phosphodiesterase isoform is over 96% identical in sequence to the human PDE4B1 isoform.

The invention further comprises a second cDNA, pRPDE90, which encodes a

novel protein of 659 amino acids, called PDE4B4. PDE4B4 has a novel N-terminal region of 17 amino acids which is not present in any other known PDE4B isoform. The remaining 642 amino acids of PDE4B4 are identical to those found in corresponding regions of the PDE4B1 and PDE4B3 isoforms. Without being bound to any particular theory, it is believed that the structures of the cDNAs encoding the PDE4B1, PDE4B3, and PDE4B4 isoforms are generated by alternative mRNA splicing and through the use of alternative promoters of the *PDE4B* gene. RNase protection and immunoblotting demonstrated the presence of mRNA and protein specific for each of the PDE4B1, PDE4B2, PDE4B3 and PDE4B4 isoforms, respectively, in a wide range of tissues, including various regions of the brain.

Since various inhibitors of cAMP phosphodiesterases have been shown to have anti-depressant and memory enhancement effects, the discovery of novel isoforms of PDE4B opens possibilities of better understanding and targeting such inhibitors to have more selective effects on the brain.

These and other features of the present invention will become apparent upon reference to the accompanying figures and upon reading the following detailed description and appended claims.

5. Brief Description of the Drawings

A more particular description of the invention briefly described above will be rendered by reference to the appended figures. These figures only provide information concerning typical embodiments of the invention and are not therefore to be considered limiting of its scope.

Figure 1 shows the structure of mRNAs encoded by the rat *PDE4B* gene. The numbers 1-4 indicate transcripts represented by the following cDNAs: 1, PDE4B1 (pRPDE89 (SEQ ID NO: 5); GenBank™ AF202732); 2, PDE4B2 (pRPDE18 (SEQ ID NO: 8); GenBank™ L27058); 3, PDE4B3 (pRPDE74 (SEQ ID NO: 9); GenBank™ U95748); 4, PDE4B4 (pRPDE90 (SEQ ID NO: 1) and pRPDE92 (SEQ ID NO: 10); GenBank™ AF202733). The heavy bar indicates sequences homologous to other PDE4 isoforms, with the strongest regions of conservation (the catalytic region and UCR1 and UCR2) indicated by the cross-hatched areas. The thin, branched lines adjacent to the numbers indicate sequence regions unique to each isoform. The thin lines merge where

the sequences of the various isoforms join the shared sequence. Small boxes indicate start codons and the asterisk indicates the common stop codon.

Figure 2 shows an alignment of the amino acid sequences of human PDE4B1 (top, SEQ ID NO: 7) and rat PDE4B1 (bottom, SEQ ID NO: 6). The sequence of human
5 PDE4B1 has been described previously (pTM72 in Bolger, *Mol. Cell Biol.* 13:6558-71 (1993), GenBank™ L20966). The sequence of PDE4B1 was deduced from the pRPDE89 cDNA.

Figure 3 shows an alignment of the amino acid sequences of rat PDE4B1 (SEQ ID NO: 6), PDE4B2 (SEQ ID NO: 8), PDE4B3 (SEQ ID NO: 9), and PDE4B4 (SEQ ID NO: 2). The sequences are derived from the following cDNAs: PDE4B1 (pRPDE89 (SEQ ID
10 NO: 5); GenBank™ AF202732); PDE4B2 (pRPDE18 (SEQ ID NO: 10); GenBank™ L27058); PDE4B3 (pRPDE74 (SEQ ID NO: 11); GenBank™ U95748); PDE4B4 (pRPDE90 and pRPDE92; GenBank™ AF202733).

Figure 4 shows the nucleotide sequence (SEQ ID NO: 1) encoding PDE4B4. The
15 sequences of two plasmids, pRPDE90 and pRPDE92, have been merged. On the merged sequence, pRPDE92 corresponds to nucleotides 1 to 1936, and pRPDE90 corresponds to nucleotides 253 to 2433. This sequence is available as GenBank™ AF202733.

Figure 5 shows the nucleotide sequence of pRPDE89 (SEQ ID NO: 5), which
20 encodes PDE4B1. This sequence is available as GenBank™ AF202732.

6. Detailed Description of the Invention

The present invention provides two novel cAMP-specific phosphodiesterase (PDE4B) isoform cDNAs. These cDNAs encode phosphodiesterases, which function in
25 the regulation of physiological processes by hydrolyzing cAMP, an intracellular signaling molecule derived from ATP.

The first cAMP-specific phosphodiesterase isoform cDNA is pRPDE90, a phosphodiesterase isolated from a rat (*Rattus norvegicus*; Sprague-Dawley strain) cerebral cortex cDNA library cloned into the Eco RI site of Lambda ZAPII, which was
30 obtained from Stratagene. This cDNA encodes a novel PDE4B isoform named PDE4B4 by the inventors in accordance with convention.

PDE4B4 is a novel PDE4B isoform comprising 659 amino acids, 642 of which are shared with the other "long;" isoforms of PDE4B: PDE4B1 and PDE4B2. The remaining 17 amino acids are found at the extreme amino-terminal end of the protein.

The second cAMP-specific phosphodiesterase isoform cDNA of the instant invention is pRPDE89, a novel rat cDNA. pRPDE89 encodes a protein comprising 736 amino acids. This protein is identical in length and 96% identical in amino acids to the human PDE4B1 isoform (712 of 736 amino acids are identical). Without being bound to any particular theory, it appears that pRPDE89 encodes the rat counterpart of the human PDE4B1 isoform of PDE4B.

The present invention provides isolated and purified nucleic acid molecules comprising nucleotides that encode the amino acid sequences of SEQ ID NOS: 2, 4, and 6. In certain embodiments, these nucleic acid molecules comprise nucleotides 262 to 2238 of SEQ ID NO: 1, nucleotides 1 to 51 of SEQ ID NO: 3, and nucleotides 325 to 2532 of SEQ ID NO: 5, respectively. The present invention also provides nucleic acid molecules that encode amino acid sequences that are greater than 90%, greater than 85%, greater than 80%, greater than 75%, and greater than 70% identical to SEQ ID NO: 4. The present invention also provides such nucleic acid molecules subcloned into plasmids; such nucleic acid molecules subcloned into prokaryotic or eukaryotic expression vectors; and such nucleic acid molecules stably or transiently incorporated into a prokaryotic or eukaryotic host cell.

The present invention also provides isolated and purified proteins comprising the amino acid sequences of SEQ ID NOS: 2 and 6 and peptides comprising the amino acid sequence of SEQ ID NO: 4. The present invention further provides antibodies that specifically recognize peptides comprising the amino acid sequence of SEQ ID NO: 4. Such antibodies may be polyclonal or monoclonal antibodies that are prepared according to methods that are well-known in the art. *See, e.g., Harlow & Lane, Antibodies: A Laboratory Manual* (1988).

Novel PDE4B isoforms such as those of the instant invention are of importance for several reasons. One reason is that the isoforms of the present invention are expressed in brain—an important potential target of PDE4 inhibitors. Indeed, cDNAs encoding numerous PDE4 isoforms have previously been isolated from brain. *See e.g., Bolger et al., Mol. Cell Biol.* 13:6558–71 (1993), *Huston et al., Biochem J.* 328:549–56 (1997),

McLaughlin et al., *J. Biol. Chem.* 268:6470–76 (1993), Bolger et al., *Gene* 149:237–44 (1993), Davis et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:3604–08 (1989), Colicelli et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:3599–3603 (1989), and Engels et al., *FEBS Lett.* 358:305–10 (1995). The brain is thus a target for many of the actions of selective PDE4 inhibitors. It is therefore important to determine exactly which PDE4 isoforms are present in the brain.

PDE4 inhibitors have several demonstrated effects in the human brain, several of which are beneficial, and others of which are harmful. Some of the potential beneficial effects of PDE4 inhibitors include a demonstrated anti-depressant action. Fleischhacker et al., *Neuropsychobiology*, 26:59–64 (1992), Eckmann et al., *Current Therapeutic Research*, 43:291–95 (1988). PDE4 inhibitors may also augment memory and other central nervous system functions. However, PDE4 inhibitors can cause nausea and trigger other gastrointestinal side effects. At least a portion of these deleterious side effects are likely mediated by the action of these drugs in the brain.

Discovery of additional isoforms of the PDE4B phosphodiesterases would open greater possibilities for developing inhibitors that could be specifically targeted at one or more isoforms. Such targeting would allow a more viable approach for utilizing the beneficial properties of these inhibitors in clinical treatment, while selectively avoiding negative side effects.

As a result, a search for novel PDE4 isoforms was initiated in rat brain. Two previously unknown PDE4 isoforms were subsequently isolated. While not being bound to any one particular theory, one of these appears to be the rat homolog of the human PDE4B1 isoform, which has been described previously in the art. Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993). The second novel isoform, called PDE4B4, has a unique 17 amino acid amino-terminal region which is not present in any other PDE4B isoform. It appears likely that PDE4B4 will be similar to other PDE4 isoforms in that it will be highly specific for cAMP and be inhibited by the prototypical PDE4 inhibitor rolipram.

It has previously been shown that the various PDE4 isoforms have different tissue expression patterns. Huston et al., *Biochem J.* 328:549–56 (1997). Indeed, it has even been shown that different isoforms encoded by the same gene may vary substantially in their tissue expression. (Bolger et al., *Mol. Cell Biol.* 13:6558–71 (1993), Bolger et al., *J. Biol. Chem.* 271:1065–71 (1996), and Bolger et al., *Gene* 149:237–44 (1994). Studies are

in progress to determine the pattern of expression of the four known rat PDE4B isoforms, with special emphasis on their expression in various regions of the brain. Such discoveries and studies create the possibility of exploiting differences in the patterns of tissue expression of the various PDE4 isoforms to "target" the effects of PDE4 inhibitors to specific regions of the brain, thus maximizing their positive effects and minimizing or negating their negative effects.

One current explanation for the divergence of the PDE4B1, PDE4B3 and PDE4B4 mRNAs is alternative mRNA splicing. This has been documented as accounting for the existence of the PDE4A and PDE4D isoforms. Bolger et al., *J.Biol.Chem.* 271:1065-71 (1996), Bolger et al., *Biochem J.* 328:539-48 (1997), and Houslay et al., *Advances in Pharmacology* 44:225-342 (1998). Consistent with this explanation, it has been shown that the point of divergence between PDE4B1, PDE4B3 and PDE4B4 corresponds with the major point of alternative mRNA splicing in the *D. melanogaster dunce* gene transcripts. It also corresponds with the major point of alternative mRNA splicing in alternatively spliced mRNAs from the human *PDE4A* (Bolger et al., *Mol. Cell Biol.* 13:6558-71 (1993)), *PDE4B* (Huston et al., *Biochem J.* 328:549-56 (1997)) and *PDE4D* (Bolger et al., *Biochem J.* 328:539-48 (1997)) genes. It also corresponds to the 5' end of an exon in the human *PDE4A* (Sullivan et al., *Biochem J.* 333:693-703 (1998)) and murine *Pde4a* (Olsen & Bolger, *Mammalian Genome* 11:41-45 (2000)) genes.

In addition, since there is no common 5' region of sequence at the 5' ends of any of these cDNAs, it appears likely that each is generated from a different transcriptional start site. It has been previously demonstrated that several murine *Pde4a* transcripts, including PDE4A5, are generated in this manner (Olsen & Bolger, *Mammalian Genome* 11:41-45 (2000)).

All references, publications, patents, patent applications, and commercial materials cited in this application are hereby incorporated by reference in their entirety.

7. Examples:

The following example is given to illustrate an embodiment which has been made within the scope of the present invention. It is to be understood that the following example is neither comprehensive nor exhaustive of the many types of embodiments which can be prepared in accordance with the present invention.

Example 1—Two Novel PDE4B Isoforms

Experimental Techniques:

Materials: A rat (*Rattus norvegicus*; Sprague-Dawley strain) cerebral cortex cDNA library, cloned into the Eco RI site of Lambda ZAPII, was obtained from
5 Stratagene. All molecular biology, biochemistry and cell culture reagents were from New England Biolabs, Life Technologies or Roche Molecular Systems unless specified otherwise.

Isolation and Analysis of cDNA Clones: Procedures were as described by Sambrook *et al.* (Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, (1989))
10 unless otherwise specified. The cDNA library was screened with a probe corresponding to nucleotides 204 to 1299 of rat PDE4B3 (pRPDE74 (SEQ ID NO: 9) GenBank™ accession number U95748; (Huston *et al.*, *Biochem J.* 328:549–56 (1997)). This region encodes the unique amino-terminal region of PDE4B3 as well as UCR1 and the majority of UCR2 (Fig. 1). Hybridization was performed with a final wash in 0.3 x SSC, 0.3%
15 SDS at 62°C. Sequencing was performed on both strands with an ABI Prism sequencer (Perkin-Elmer) according to the manufacturer's instructions. Alignments were generated with the Gap and Lineup programs of the Wisconsin Package of UNIX sequence software programs (Oxford Molecular Group).

Results:

20 To obtain cDNAs encoding PDE4B isoforms, a rat cortex cDNA library was screened with a probe corresponding to UCR1 and UCR2 of rat PDE4B3 (Huston *et al.*, *Biochem. J.* 328:549–56 (1997)). This probe was designed to detect all "long" (i.e., UCR1-containing) PDE4B isoforms. cDNAs encoding two different PDE4B isoforms were detected in the screen (see Fig. 1). One cDNA clone, called pRPDE89 (SEQ ID
25 NO: 5), encoded a protein of 736 amino acids (SEQ ID NO: 6). This isoform was identical in length and had greater than 96% amino acid identity (712/736 amino acids identical, Fig. 2) with the human PDE4B1 isoform (SEQ ID NO: 7). Bolger *et al.*, *Mol. Cell Biol.* 13:6558–71 (1993). It was therefore concluded that pRPDE89 encodes the rat PDE4B1 isoform.

30 Also detected in the screen was a cDNA clone, called pRPDE90 (SEQ ID NO: 1), which encoded the complete open reading frame of a novel PDE4B isoform. This new isoform was called PDE4B4, using the accepted nomenclature. Beavo, *Physiol. Rev.* 75:725–48 (1995). The PDE4B4 protein consists of 659 amino acids (SEQ ID NO: 2), 17

of which are located at the extreme amino-terminal end of the protein and show no detectable homology to any previously cloned PDE4B sequence (SEQ ID NOS: 3, 4). The remaining 642 amino acids are identical to the corresponding regions of the "long" PDE4B isoforms PDE4B1 and PDE4B3 (Fig. 3). The nucleotide sequences of the common regions of PDE4B1, PDE4B3 and PDE4B4 are also identical. The sequence of the novel region of PDE4B4 was confirmed by the sequence of another clone isolated in the screen, called pRPDE92 (SEQ ID NO: 10), which completely overlapped the novel region of pRPDE90 and contained sequence of an additional portion of the 5' untranslated region of the mRNA.

The invention may be embodied in other specific forms without departing from its essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS:

1. An isolated and purified nucleic acid molecule comprising nucleotides encoding the amino acid sequence of SEQ ID NO: 2.
2. The nucleic acid molecule of Claim 1, comprising nucleotides 262 to 2238 of SEQ ID NO: 1.
3. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is subcloned into a plasmid.
4. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is subcloned into a prokaryotic or eukaryotic expression vector.
5. The nucleic acid molecule of Claim 1, wherein said nucleic acid molecule is stably or transiently incorporated into a prokaryotic or eukaryotic host cell.
6. An isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 2.
7. An isolated and purified nucleic acid molecule comprising nucleotides which code for the amino acid sequence of SEQ ID NO: 4.
8. The nucleic acid molecule of Claim 7, comprising the nucleotide sequence of SEQ ID NO: 3.
9. An isolated and purified nucleic acid molecule comprising a nucleotide sequence that encodes an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 4.
10. An isolated and purified nucleic acid molecule comprising a nucleotide sequence that encodes an amino acid sequence that is at least 75% identical to the amino acid sequence of SEQ ID NO: 4.
11. An isolated and purified peptide comprising the amino acid sequence of SEQ ID NO: 4.
12. An antibody that specifically recognizes the peptide of claim 11.
13. An isolated and purified nucleic acid molecule comprising nucleotides encoding the amino acid sequence of SEQ ID NO: 6.
14. The nucleic acid molecule of Claim 13, comprising nucleotide 325 to 2532 of SEQ ID NO: 5.
15. The nucleic acid molecule of Claim 13, wherein said nucleic acid molecule is subcloned into a plasmid.
16. The nucleic acid molecule of Claim 13, wherein said nucleic acid molecule is

subcloned into a prokaryotic or eukaryotic expression vector.

17. The nucleic acid molecule of Claim 14, wherein said nucleic acid molecule is stably or transiently incorporated into a prokaryotic or eukaryotic host cell.
18. An isolated and purified protein comprising the amino acid sequence of SEQ ID NO: 6.

5

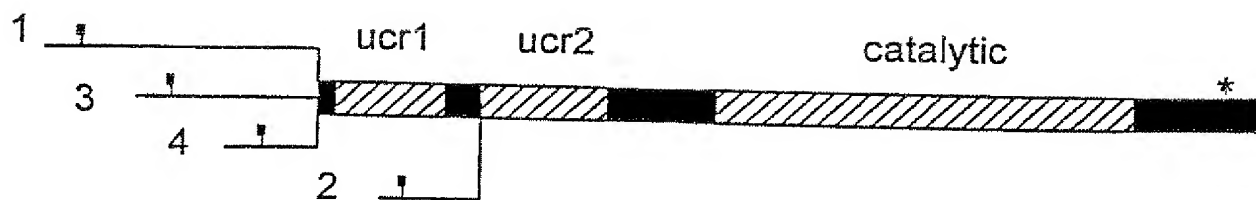


Fig. 2 (two pages in length)

1	MKKSRSVMTVMADDNVVDYFECSLSKSYSSSSNTLGIDLWRGRRCCSGNL	50
1	MKKSRSVMAVTADDNLKDYFECSLSKSYSSSSYTLGIDLWRGRRCCSGNL	50
51	QLPPLSQRQSERARTPEGDGISRPTTLPLTTPLPSIAITTVSQECFDVENG	100
51	QLPPLSQRQSERARTPEGDGISRPTTLPLTTPLPSIAITTVSQECFDVENG	100
101	PSPGRSPDPQASSSAGLVLHATFPGHSQRRESFLYRSDSDYDLSPKAMS	150
101	PSPGRSPDPQASSSSGLVLHAAFPFGHSQRRESFLYRSDSDYDLSPKAMS	150
151	RNSSLPSEQHGDDLIVTPFAQVLASLRVRNNFTILTNLHGTSNKRSPAA	200
151	RNSSLPSEQHGDDLIVTPFAQVLASLRVRNNFTLLTNLHGAPNKRSPAA	200
201	SQPPVSRVNPQEESYQKLAMETLEELDWCLDQLETIQTYRSVSEMASNKF	250
201	SQAPVTRVSLQEESYQKLAMETLEELDWCLDQLETIQTYRSVSEMASNKF	250
251	KRMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSTQKDREKKK	300
251	KRMLNRELTHLSEMSRSGNQVSEYISNTFLDKQNDVEIPSTQKDREKKK	300
301	KQQLMTQISGVKMLMHSSSLNNTSISRFGVNTENEDHLAKELEDLNKWGL	350
301	KQQLMTQISGVKMLMHSSSLNNTSISRFGVNTENEDHLAKELEDLNKWGL	350
351	NIFNVAGYSHNRPLTCIMYAIFQERDLLKTFRISSDTFITYMMTLEDHYH	400
351	NIFNVAGYSHNRPLTCIMYAIFQERDLLKTFKISSDTFVITYMMTLEDHYH	400
401	SDVAYHNSLHAADVAQSTHVLLSTPALDAVFTDLEILAAIFAAAIHDVDH	450
401	SDVAYHNSLHAADVAQSTHVLLSTPALDAVFTDLEILAAIFAAAIHDVDH	450
451	PGVSNQFLINTNSELALMYNDESVLENHHLAVGFKLLQEEHCDIFMNLTK	500
451	PGVSNQFLINTNSELALMYNDESVLENHHLAVGFKLLQEEHCDIFQNLTK	500
501	KQRQTLRKMVIDMVLATDMSKHMSLLADLKTMTVETKKVTSSGVLLLDNYT	550
501	KQRQTLRKMVIDMVLATDMSKHMSLLADLKTMTVETKKVTSSGVLLLDNYT	550
551	DRIQVLRNMVHCADLSNPTKSLELYRQWTDRIEEFFQOGDKERERGMEI	600
551	DRIQVLRNMVHCADLSNPTKSLELYRQWTDRIEEFFQOGDKERERGMEI	600

Fig. 3 (two pages in length)

	1		50
PDE4B3MTAKN SSKELPASES EVCIKTFKEQ MRLELELPKL		
PDE4B1	MKKSRSVMAV TADDNLKDYF ECSSLKSYSS SSYTLGIDLW RGRRCSSGNL		
PDE4B4		
PDE4B2		
	51		100
PDE4B3	PGNRPTSPKI SPRSSPRNSP CFFRKLLVNK SIRQRRRFTV AHTCFDVENG		
PDE4B1	QLPPLSQRQS ERARTPEGDG ISRPTTLPLT TLPSTAITTV SQECFDVENG		
PDE4B4MLH VNDLPPRRH SWICFDVENG		
PDE4B2		
	101		150
PDE4B3	PSPGRSPLDP QASSSSGLVL HAAFPGHSQR RESFLYRSDS DYDLSPKAMS		
PDE4B1	PSPGRSPLDP QASSSSGLVL HAAFPGHSQR RESFLYRSDS DYDLSPKAMS		
PDE4B4	PSPGRSPLDP QASSSSGLVL HAAFPGHSQR RESFLYRSDS DYDLSPKAMS		
PDE4B2		
	151		200
PDE4B3	RNSSLPSEQH GDDLIVTPFA QVLASLRIVR NNFTLLTNLH GAPNKRSPAA		
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	301		350
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Fig. 4

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Fig. 5

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360

365

His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr
 370 375 380

Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn
 385 390 395 400

His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp
 405 410 415

Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met
 420 425 430

Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu
 435 440 445

Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser
 450 455 460

Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg
 465 470 475 480

Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu
 485 490 495

Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln
 500 505 510

Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp
 515 520 525

Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr
 530 535 540

Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp
 545 550 555 560

Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln
 565 570 575

Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg
 580 585 590

Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu
 595 600 605

Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr
 610 615 620

Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp
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Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu
 645 650 655

Ile Asp Thr

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 <211> 51
 <212> DNA
 <213> Rattus norvegicus

<220>
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 <222> (1)..(51)

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 Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
 1 5 10 15
 tgc
 Cys 51

<210> 4
 <211> 17
 <212> PRT
 <213> Rattus norvegicus

<400> 4
 Met Leu His Val Asn Asp Leu Pro Pro Pro Arg Arg His Ser Trp Ile
 1 5 10 15
 Cys

<210> 5
 <211> 3022
 <212> DNA
 <213> Rattus norvegicus

<220>
 <221> CDS
 <222> (325)..(2532)

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tgggcacgca gggctgcgtg taatcctcca gcctcgggtg agggaggctg cagcgagcgc      180
cggctggcag taagggttct tctgcaaaag tcccctgcgg ttgcgcgcgt ggagtgccgg      240
ggagctcggc caggtctagt ctgcagtcag caaagctgca gcaaacagca gacatctcca      300
gaggagctgt ttgccacatc tata atg aag aaa agt agg agt gtg atg gcc      351
                        Met Lys Lys Ser Arg Ser Val Met Ala
                        1                      5

gtg act gca gat gat aat ctt aag gac tat ttt gaa tgt agc ttg agt      399
Val Thr Ala Asp Asp Asn Leu Lys Asp Tyr Phe Glu Cys Ser Leu Ser
10                      15                      20                      25

aaa tcc tac agt tct tcc agt tat acc ctt ggg att gac ctc tgg aga      447
Lys Ser Tyr Ser Ser Ser Ser Tyr Thr Leu Gly Ile Asp Leu Trp Arg
                      30                      35                      40

ggc aga agg tgc tgt tca gga aac tta cag ttg cca cca ttg tcc cag      495
Gly Arg Arg Cys Cys Ser Gly Asn Leu Gln Leu Pro Pro Leu Ser Gln
                      45                      50                      55

aga caa agt gaa agg gca agg aca cct gag gga gat ggc att tcc agg      543
Arg Gln Ser Glu Arg Ala Arg Thr Pro Glu Gly Asp Gly Ile Ser Arg
                      60                      65                      70

cca acc acg cta cct ttg acg aca ctt ccc agc att gct ata aca act      591
Pro Thr Thr Leu Pro Leu Thr Thr Leu Pro Ser Ile Ala Ile Thr Thr
75                      80                      85

gta agc cag gag tgc ttt gat gtg gaa aat ggc cct tct cca ggt cgg      639
Val Ser Gln Glu Cys Phe Asp Val Glu Asn Gly Pro Ser Pro Gly Arg
90                      95                      100                      105

agc cca ctg gac cct caa gcc agc tct tct tca gga ctg gta ctt cat      687
Ser Pro Leu Asp Pro Gln Ala Ser Ser Ser Ser Gly Leu Val Leu His
                      110                      115                      120

gcc gcc ttc cct ggg cac agc caa cgc aga gag tct ttt ctc tac aga      735
Ala Ala Phe Pro Gly His Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg
125                      130                      135

tcc gac agc gac tat gac ttg tca cca aaa gcg atg tca agg aac tcc      783
Ser Asp Ser Asp Tyr Asp Leu Ser Pro Lys Ala Met Ser Arg Asn Ser
140                      145                      150

tca ctt ccc agc gaa caa cac ggc gat gac ctg att gtc act cct ttt      831
Ser Leu Pro Ser Glu Gln His Gly Asp Asp Leu Ile Val Thr Pro Phe
155                      160                      165

gcc cag gtt ctt gcc agc ttg cga agc gta aga aac aat ttc acc ctg      879
Ala Gln Val Leu Ala Ser Leu Arg Ser Val Arg Asn Asn Phe Thr Leu
170                      175                      180                      185

ctg aca aac ctt cac gga gca ccg aac aag agg tgc cca gcg gct agt      927
Leu Thr Asn Leu His Gly Ala Pro Asn Lys Arg Ser Pro Ala Ala Ser

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190	195	200	
cag gct cca gtc acc aga gtc agc ctg caa gaa gaa tca tat cag aaa Gln Ala Pro Val Thr Arg Val Ser Leu Gln Glu Glu Ser Tyr Gln Lys 205 210 215			975
cta gca atg gag acg ctg gag gaa cta gac tgg tgc cta gac cag cta Leu Ala Met Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu 220 225 230			1023
gag acc atc cag acc tac cgc tct gtc agc gag atg gct tca aac aag Glu Thr Ile Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys 235 240 245			1071
ttc aaa agg atg ctg aac cgg gag ctg aca cac ctc tca gag atg agc Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser 250 255 260 265			1119
aga tca ggg aac caa gtg tct gaa tac att tgc aac acg ttc tta gac Arg Ser Gly Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp 270 275 280			1167
aag cag aac gat gtg gaa atc cca tct ccc acc cag aag gac agg gag Lys Gln Asn Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu 285 290 295			1215
aag aag aag aag cag cag ctc atg acc cag ata agt gga gtg aag aaa Lys Lys Lys Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys 300 305 310			1263
ctg atg cac agc tca agc ctg aac aac aca agc atc tca cgc ttt gga Leu Met His Ser Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly 315 320 325			1311
gtc aac acg gaa aat gag gat cat cta gcc aag gag ctg gaa gac ctg Val Asn Thr Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu 330 335 340 345			1359
aac aaa tgg ggc ctt aac atc ttc aac gtg gct ggg tac tcc cat aat Asn Lys Trp Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn 350 355 360			1407
cgg ccc ctc aca tgc atc atg tac gcc att ttc cag gaa aga gac ctt Arg Pro Leu Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu 365 370 375			1455
cta aag acg ttt aaa atc tcc tcc gac acc ttc gta acc tac atg atg Leu Lys Thr Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met 380 385 390			1503
act tta gaa gac cat tac cat tct gat gtg gcg tat cac aac agc ctg Thr Leu Glu Asp His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu 395 400 405			1551
cac gct gct gac gtg gcc cag tca acg cac gtt ctc ctc tct acg cca His Ala Ala Asp Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro 410 415 420 425			1599
gca ctg gat gct gtc ttc aca gac ctg gaa atc ctg gct gcc att ttt Ala Leu Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe 430 435 440			1647

gca gct gcc atc cat gat gtt gat cat cct gga gtc tcc aat cag ttt Ala Ala Ala Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe 445 450 455	1695
ctc atc aat aca aat tcc gaa ctt gct ttg atg tat aat gac gaa tct Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser 460 465 470	1743
gtg ctg gaa aac cat cac ctc gct gtg gga ttc aag ctc ctt caa gag Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu 475 480 485	1791
gaa cat tgc gac atc ttt cag aat ctt acc aag aag caa cgc cag aca Glu His Cys Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr 490 495 500 505	1839
ctc agg aaa atg gtg att gac atg gtg tta gca act gat atg tcc aag Leu Arg Lys Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys 510 515 520	1887
cac atg agc ctc ctg gct gac ctt aaa acg atg gta gaa acc aaa aag His Met Ser Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys 525 530 535	1935
gtg acg agc tcc ggt gtt ctc ctc ctg gac aac tat act gac cgg ata Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile 540 545 550	1983
cag gtt ctt cgc aac atg gta cat tgt gca gac ctg agc aac cct acc Gln Val Leu Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr 555 560 565	2031
aag tcc ttg gag ttg tat cgg caa tgg act gat cgc atc atg gag gag Lys Ser Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu 570 575 580 585	2079
ttt ttc caa cag gga gac aaa gaa cgg gag agg gga atg gag att agc Phe Phe Gln Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser 590 595 600	2127
cca atg tgt gat aaa cac aca gct tct gtg gaa aag tcc cag gtt ggt Pro Met Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly 605 610 615	2175
ttc att gac tac att gtc cat cca ttg tgg gag acc tgg gca gac ctg Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu 620 625 630	2223
gtt cag cct gat gct caa gac att ttg gac aca cta gaa gat aac agg Val Gln Pro Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg 635 640 645	2271
aac tgg tac cag agt atg att ccc cag agc ccc tct cca cca ctg gac Asn Trp Tyr Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp 650 655 660 665	2319
gag agg agc agg gac tgc caa ggc ctt atg gag aag ttt cag ttc gaa Glu Arg Ser Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu 670 675 680	2367

ctg acc ctt gaa gaa gag gat tct gaa gga ccg gaa aag gag gga gaa 2415
 Leu Thr Leu Glu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu
 685 690 695

ggc ccc aac tat ttc agc agc aca aag aca ctt tgt gtg atc gat cca 2463
 Gly Pro Asn Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro
 700 705 710

gag aac agg gat tct ctg gaa gag act gac ata gac att gcc aca gaa 2511
 Glu Asn Arg Asp Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu
 715 720 725

gac aag tct ctg atc gac aca taatctccct ctgtgtggag gtgaacattc 2562
 Asp Lys Ser Leu Ile Asp Thr
 730 735

tatccttgac gagcatgcc a gctgagtggg agggcccacc taccagagcc aaggcctgca 2622

caaaacaaag gccacctggc ctttgagttt acttgagttt ggagccagaa tgcaaggccg 2682

tgaagcaa at agcagttccg tgctgccttg ccttgccggc gagcttgggc gagacccgca 2742

gctgtagtag aagccagttc ccagcacagc taaatggctt gaaaacagag gacagaaagc 2802

tgagagattg ctctgcaata ggtgttgagg ggctgtcccg acaggtgact gaactcacta 2862

acaacttcat ctataaatct caccatcct gttgtctgcc aacctgtgtg ccttttttgt 2922

aaaatgtttt cgtgtctttg aaatgcctgt tgaatatcta gagtttagta cctccttcta 2982

caaacttttt tgagtctttc tgggaaaaaa aaacctgcag 3022

<210> 6
 <211> 736
 <212> PRT
 <213> Rattus norvegicus

<400> 6

Met Lys Lys Ser Arg Ser Val Met Ala Val Thr Ala Asp Asp Asn Leu
 1 5 10 15

Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser Ser
 20 25 30

Tyr Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly
 35 40 45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg
 50 55 60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr
 65 70 75 80

Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp

85

90

95

Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala
 100 105 110

Ser Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro Gly His Ser
 115 120 125

Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu
 130 135 140

Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His
 145 150 155 160

Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu
 165 170 175

Arg Ser Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His Gly Ala
 180 185 190

Pro Asn Lys Arg Ser Pro Ala Ala Ser Gln Ala Pro Val Thr Arg Val
 195 200 205

Ser Leu Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu
 210 215 220

Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg
 225 230 235 240

Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg
 245 250 255

Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser
 260 265 270

Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile
 275 280 285

Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln Gln Leu
 290 295 300

Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu
 305 310 315 320

Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp
 325 330 335

His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile
 340 345 350

Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met
 355 360 365

Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Lys Ile Ser
 370 375 380

Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu Asp His Tyr His
 385 390 395 400

Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
 405 410 415

Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
 420 425 430

Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
 435 440 445

Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
 450 455 460

Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
 465 470 475 480

Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Gln
 485 490 495

Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
 500 505 510

Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
 515 520 525

Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
 530 535 540

Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
 545 550 555 560

His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
 565 570 575

Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
 580 585 590

Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
 595 600 605

Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
 610 615 620

Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
 625 630 635 640

Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
 645 650 655

Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser Arg Asp Cys Gln
 660 665 670

Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Glu Asp
 675 680 685

Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn Tyr Phe Ser Ser
 690 695 700

Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Glu
 705 710 715 720

Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Leu Ile Asp Thr
 725 730 735

<210> 7
 <211> 736
 <212> PRT
 <213> Homo sapiens

<400> 7

Met Lys Lys Ser Arg Ser Val Met Thr Val Met Ala Asp Asp Asn Val
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Lys Asp Tyr Phe Glu Cys Ser Leu Ser Lys Ser Tyr Ser Ser Ser Ser
 20 25 30

Asn Thr Leu Gly Ile Asp Leu Trp Arg Gly Arg Arg Cys Cys Ser Gly
 35 40 45

Asn Leu Gln Leu Pro Pro Leu Ser Gln Arg Gln Ser Glu Arg Ala Arg
 50 55 60

Thr Pro Glu Gly Asp Gly Ile Ser Arg Pro Thr Thr Leu Pro Leu Thr

65	70	75	80
Thr Leu Pro Ser Ile Ala Ile Thr Thr Val Ser Gln Glu Cys Phe Asp	85	90	95
Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln Ala	100	105	110
Ser Ser Ser Ala Gly Leu Val Leu His Ala Thr Phe Pro Gly His Ser	115	120	125
Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Leu	130	135	140
Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln His	145	150	155
Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu	165	170	175
Arg Ser Val Arg Asn Asn Phe Thr Ile Leu Thr Asn Leu His Gly Thr	180	185	190
Ser Asn Lys Arg Ser Pro Ala Ala Ser Gln Pro Pro Val Ser Arg Val	195	200	205
Asn Pro Gln Glu Glu Ser Tyr Gln Lys Leu Ala Met Glu Thr Leu Glu	210	215	220
Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile Gln Thr Tyr Arg	225	230	235
Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg Met Leu Asn Arg	245	250	255
Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser	260	265	270
Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn Asp Val Glu Ile	275	280	285
Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys Lys Gln Gln Leu	290	295	300
Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His Ser Ser Ser Leu	305	310	315
Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr Glu Asn Glu Asp	325	330	335
His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp Gly Leu Asn Ile	340	345	350
Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu Thr Cys Ile Met	355	360	365
Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr Phe Arg Ile Ser	370	375	380
Ser Asp Thr Phe Ile Thr Tyr Met Met Thr Leu Glu Asp His Tyr His	385	390	395
			400

Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala Asp Val Ala Gln
 405 410 415
 Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp Ala Val Phe Thr
 420 425 430
 Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala Ile His Asp Val
 435 440 445
 Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu
 450 455 460
 Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu Asn His His Leu
 465 470 475 480
 Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys Asp Ile Phe Met
 485 490 495
 Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys Met Val Ile Asp
 500 505 510
 Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser Leu Leu Ala Asp
 515 520 525
 Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser Ser Gly Val Leu
 530 535 540
 Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu Arg Asn Met Val
 545 550 555 560
 His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu Glu Leu Tyr Arg
 565 570 575
 Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln Gln Gly Asp Lys
 580 585 590
 Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys Asp Lys His Thr
 595 600 605
 Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp Tyr Ile Val His
 610 615 620
 Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro Asp Ala Gln Asp
 625 630 635 640
 Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr Gln Ser Met Ile
 645 650 655
 Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Gln Asn Arg Asp Cys Gln
 660 665 670
 Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu Asp Glu Glu Asp
 675 680 685
 Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly His Ser Tyr Phe Ser Ser
 690 695 700
 Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg Asp Ser Leu Gly
 705 710 715 720

Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser Pro Val Asp Thr
 725 730 735

<210> 8
 <211> 564
 <212> PRT
 <213> Rattus norvegicus

<400> 8

Met Lys Glu Gln Gly Gly Thr Val Ser Gly Ala Gly Ser Ser Arg Gly
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Gly Gly Asp Ser Ala Met Ala Ser Leu Gln Pro Leu Gln Pro Asn Tyr
 20 25 30

Leu Ser Val Cys Leu Phe Ala Glu Ser Tyr Gln Lys Leu Ala Met
 35 40 45

Glu Thr Leu Glu Glu Leu Asp Trp Cys Leu Asp Gln Leu Glu Thr Ile
 50 55 60

Gln Thr Tyr Arg Ser Val Ser Glu Met Ala Ser Asn Lys Phe Lys Arg
 65 70 75 80

Met Leu Asn Arg Glu Leu Thr His Leu Ser Glu Met Ser Arg Ser Gly
 85 90 95

Asn Gln Val Ser Glu Tyr Ile Ser Asn Thr Phe Leu Asp Lys Gln Asn
 100 105 110

Asp Val Glu Ile Pro Ser Pro Thr Gln Lys Asp Arg Glu Lys Lys Lys
 115 120 125

Lys Gln Gln Leu Met Thr Gln Ile Ser Gly Val Lys Lys Leu Met His
 130 135 140

Ser Ser Ser Leu Asn Asn Thr Ser Ile Ser Arg Phe Gly Val Asn Thr
 145 150 155 160

Glu Asn Glu Asp His Leu Ala Lys Glu Leu Glu Asp Leu Asn Lys Trp
 165 170 175

Gly Leu Asn Ile Phe Asn Val Ala Gly Tyr Ser His Asn Arg Pro Leu
 180 185 190

Thr Cys Ile Met Tyr Ala Ile Phe Gln Glu Arg Asp Leu Leu Lys Thr
 195 200 205

Phe Lys Ile Ser Ser Asp Thr Phe Val Thr Tyr Met Met Thr Leu Glu
 210 215 220

Asp His Tyr His Ser Asp Val Ala Tyr His Asn Ser Leu His Ala Ala
 225 230 235 240

Asp Val Ala Gln Ser Thr His Val Leu Leu Ser Thr Pro Ala Leu Asp
 245 250 255

Ala Val Phe Thr Asp Leu Glu Ile Leu Ala Ala Ile Phe Ala Ala Ala
 260 265 270

Ile His Asp Val Asp His Pro Gly Val Ser Asn Gln Phe Leu Ile Asn
 275 280 285
 Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn Asp Glu Ser Val Leu Glu
 290 295 300
 Asn His His Leu Ala Val Gly Phe Lys Leu Leu Gln Glu Glu His Cys
 305 310 315 320
 Asp Ile Phe Gln Asn Leu Thr Lys Lys Gln Arg Gln Thr Leu Arg Lys
 325 330 335
 Met Val Ile Asp Met Val Leu Ala Thr Asp Met Ser Lys His Met Ser
 340 345 350
 Leu Leu Ala Asp Leu Lys Thr Met Val Glu Thr Lys Lys Val Thr Ser
 355 360 365
 Ser Gly Val Leu Leu Leu Asp Asn Tyr Thr Asp Arg Ile Gln Val Leu
 370 375 380
 Arg Asn Met Val His Cys Ala Asp Leu Ser Asn Pro Thr Lys Ser Leu
 385 390 395 400
 Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile Met Glu Glu Phe Phe Gln
 405 410 415
 Gln Gly Asp Lys Glu Arg Glu Arg Gly Met Glu Ile Ser Pro Met Cys
 420 425 430
 Asp Lys His Thr Ala Ser Val Glu Lys Ser Gln Val Gly Phe Ile Asp
 435 440 445
 Tyr Ile Val His Pro Leu Trp Glu Thr Trp Ala Asp Leu Val Gln Pro
 450 455 460
 Asp Ala Gln Asp Ile Leu Asp Thr Leu Glu Asp Asn Arg Asn Trp Tyr
 465 470 475 480
 Gln Ser Met Ile Pro Gln Ser Pro Ser Pro Pro Leu Asp Glu Arg Ser
 485 490 495
 Arg Asp Cys Gln Gly Leu Met Glu Lys Phe Gln Phe Glu Leu Thr Leu
 500 505 510
 Glu Glu Glu Asp Ser Glu Gly Pro Glu Lys Glu Gly Glu Gly Pro Asn
 515 520 525
 Tyr Phe Ser Ser Thr Lys Thr Leu Cys Val Ile Asp Pro Glu Asn Arg
 530 535 540
 Asp Ser Leu Glu Glu Thr Asp Ile Asp Ile Ala Thr Glu Asp Lys Ser
 545 550 555 560
 Leu Ile Asp Thr

<210> 9
 <211> 721
 <212> PRT
 <213> Rattus norvegicus

<400> 9

Met Thr Ala Lys Asn Ser Ser Lys Glu Leu Pro Ala Ser Glu Ser Glu
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 Val Cys Ile Lys Thr Phe Lys Glu Gln Met Arg Leu Glu Leu Glu Leu
 20 25 30
 Pro Lys Leu Pro Gly Asn Arg Pro Thr Ser Pro Lys Ile Ser Pro Arg
 35 40 45
 Ser Ser Pro Arg Asn Ser Pro Cys Phe Phe Arg Lys Leu Leu Val Asn
 50 55 60
 Lys Ser Ile Arg Gln Arg Arg Arg Phe Thr Val Ala His Thr Cys Phe
 65 70 75 80
 Asp Val Glu Asn Gly Pro Ser Pro Gly Arg Ser Pro Leu Asp Pro Gln
 85 90 95
 Ala Ser Ser Ser Ser Gly Leu Val Leu His Ala Ala Phe Pro Gly His
 100 105 110
 Ser Gln Arg Arg Glu Ser Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp
 115 120 125
 Leu Ser Pro Lys Ala Met Ser Arg Asn Ser Ser Leu Pro Ser Glu Gln
 130 135 140
 His Gly Asp Asp Leu Ile Val Thr Pro Phe Ala Gln Val Leu Ala Ser
 145 150 155 160
 Leu Arg Ile Val Arg Asn Asn Phe Thr Leu Leu Thr Asn Leu His Gly
 165 170 175
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INTERNATIONAL SEARCH REPORT

International application No.
PCT US00/34045

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 9/16, 9/22, 1/20, 15/00, 5/00; C07H 21/04

US CL : 435/196, 199, 252.3, 320.1, 325; 536.23.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/196, 199, 252.3, 320.1, 325; 536.23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MONACO, L. et al. Structure of Two Rat Genes Coding for Closely Related Rolipram-sensitive cAMP Phosphodiesterases. MULTIPLE mRNA VARIANTS ORIGINATE FROM ALTERNATE SPLICING AND MULTIPLE START SITES. J. Biol. Chem. 07 January 1994, Vol. 269, No. 1, pages 347-357, see the entire document, especially Fig. 2 to Fig. 5.	1-18
Y	HUSTON, E. et al. Molecular cloning and transient expression in COS7 cells of a novel human PDE4B cAMP-specific phosphodiesterase, HSPDE4B3. Biochem. J. 1997, Vol. 328, pages 549-558, see the entire document.	1-18

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

"	Special categories of cited documents	"I"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

13 MARCH 2001

Date of mailing of the international search report

06 APR 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
Dorinda Loupence For
TEKCHAND SAIDHA

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34045

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

West search, stn search in files medline, caplus, embase, biosis, biotechds and others. Search terms used : human or mammalian phosphodiesterase, and gene or dna or rna or nucleic acid? and others. Issued US patent, EST, genebank and protein data bases search for the claimed SEQ ID NOS.